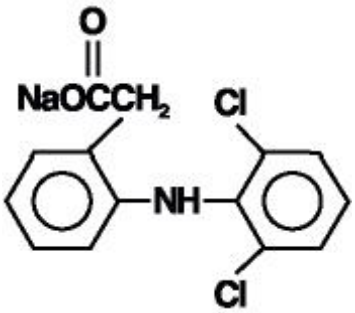
VOLTAREN - diclofenac sodium solution
Novartis Pharmaceuticals Corporation

VOLTAREN OPHTHALMIC®
(diclofenac sodium ophthalmic solution) 0.1%
Sterile Ophthalmic Solution
Rx only
Prescribing Information

DESCRIPTION

Voltaren Ophthalmic (diclofenac sodium ophthalmic solution) 0.1% solution is a sterile, topical, nonsteroidal, anti-inflammatory product for ophthalmic use. Diclofenac sodium is designated chemically as 2-[(2,6-dichlorophenyl)amino] benzeneacetic acid, monosodium salt, with an empirical formula of $C_{14}H_{10}Cl_2NO_2Na$. The structural formula of diclofenac sodium is:



Voltaren Ophthalmic is available as a sterile solution which contains diclofenac sodium 0.1% (1 mg/mL).
Inactive Ingredients: polyoxyl 35 castor oil, Boric acid, tromethamine, sorbic acid (2 mg/mL), edetate disodium (1 mg/mL), and purified water.
Diclofenac sodium is a faintly yellow-white to light-beige, slightly hygroscopic crystalline powder. It is freely soluble in methanol, sparingly soluble in water, very slightly soluble in acetonitrile, and insoluble in chloroform and in 0.1N hydrochloric acid. Its molecular weight is 318.14. Voltaren Ophthalmic 0.1% is an iso-osmotic solution with an osmolality of about 300 mOsmol/1000 g, buffered at approximately pH 7.2. Voltaren Ophthalmic solution has a faint characteristic odor of castor oil.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Diclofenac sodium is one of a series of phenylacetic acids that has demonstrated anti-inflammatory and analgesic properties in pharmacological studies. It is thought to inhibit the enzyme cyclooxygenase, which is essential in the biosynthesis of prostaglandins.

Animal Studies

Prostaglandins have been shown in many animal models to be mediators of certain kinds of intraocular inflammation. In studies performed in animal eyes, prostaglandins have been shown to produce disruption of the blood-aqueous humor barrier, vasodilation, increased vascular permeability, leukocytosis, and increased intraocular pressure.

Pharmacokinetics

Results from a bioavailability study established that plasma levels of diclofenac following ocular instillation of two drops of Voltaren Ophthalmic to each eye were below the limit of quantification (10 ng/mL) over a 4-hour period. This study suggests that limited, if any, systemic absorption occurs with Voltaren Ophthalmic.

Clinical Trials

Postoperative Anti-Inflammatory Effects

In two double-masked, controlled, efficacy studies of postoperative inflammation, a total of 206 cataract patients were treated with Voltaren Ophthalmic and 103 patients were treated with vehicle placebo. Voltaren Ophthalmic was favored over vehicle placebo over a 2-week period for the clinical assessments of inflammation as measured by anterior chamber cells and flare.
In double-masked, controlled studies of corneal refractive surgery (radial keratotomy (RK) and laser photorefractive keratectomy (PRK)) patients were treated with Voltaren Ophthalmic and/or vehicle placebo. The efficacy of Voltaren Ophthalmic given before and shortly after surgery was favored over vehicle placebo during the 6-hour period following surgery for the clinical assessments of pain and photophobia. Patients were permitted to use a hydrogel soft contact lens with Voltaren Ophthalmic for up to three days after PRK.

INDICATIONS AND USAGE

Voltaren Ophthalmic is indicated for the treatment of postoperative inflammation in patients who have undergone cataract extraction and for the temporary relief of pain and photophobia in patients undergoing corneal refractive surgery.

CONTRAINDICATIONS
Voltaren Ophthalmic is contraindicated in patients who are hypersensitive to any component of the medication.

WARNINGS
The refractive stability of patients undergoing corneal refractive procedures and treated with Voltaren has not been established. Patients should be monitored for a year following use in this setting.
With some nonsteroidal anti-inflammatory drugs, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.
There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory agents. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

PRECAUTIONS

General
All topical nonsteroidal anti-inflammatory drugs (NSAIDs) may slow or delay healing. Topical corticosteroids are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
Use of topical NSAIDs may result in keratitis. In some susceptible patients continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal infiltrates, corneal erosion, corneal ulceration, and corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs and should be closely monitored for corneal health.
Postmarketing experience with topical NSAIDs suggests that patients experiencing complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface disease (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period-of-time may be at increased risk for corneal adverse events, which may become sight threatening. Topical NSAIDs should be used with caution in these patients.
Postmarketing experience with topical NSAIDs also suggests that use more than 24 hours prior to surgery or use beyond 14 days post surgery may increase patient risk for occurrence and severity of corneal adverse events.
It is recommended that Voltaren Ophthalmic, like other NSAIDs, be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.
Results from clinical studies indicate that Voltaren Ophthalmic has no significant effect upon ocular pressure. However, elevations in intraocular pressure may occur following cataract surgery.

Information for Patients
Except for the use of a bandage hydrogel soft contact lens during the first 3 days following refractive surgery, Voltaren Ophthalmic should not be used by patients currently wearing soft contact lenses due to adverse events that have occurred in other circumstances.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term carcinogenicity studies in rats given Voltaren in oral doses up to 2 mg/kg/day (approximately 500 times the human topical ophthalmic dose) revealed no significant increases in tumor incidence. A 2-year carcinogenicity study conducted in mice employing oral Voltaren up to 2 mg/kg/day did not reveal any oncogenic potential. Voltaren did not show mutagenic potential in various mutagenicity studies including the Ames test. Voltaren administered to male and female rats at 4 mg/kg/day (approximately 1000 times the human topical ophthalmic dose) did not affect fertility.

Geriatric Use
No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

PREGNANCY

Teratogenic Effects
Pregnancy Category C. Reproduction studies performed in mice at oral doses up to 5,000 times (20 mg/kg/day) and in rats and rabbits at oral doses up to 2,500 times (10 mg/kg/day) the human topical dose have revealed no evidence of teratogenicity due to Voltaren despite the induction of maternal toxicity and fetal toxicity. In rats, maternally toxic doses were associated with dystocia, prolonged gestation, reduced fetal weights and growth, and reduced fetal survival. Voltaren has been shown to cross the placental barrier in mice and rats.
There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Non-teratogenic Effects
Because of the known effects of prostaglandin biosynthesis-inhibiting drugs on the fetal cardiovascular system (closure of ductus arteriosus), the use of Voltaren Ophthalmic during late pregnancy should be avoided.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Clinical Practice
The following events have been identified during postmarketing use of topical diclofenac sodium ophthalmic solution, 0.1% in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to topical diclofenac sodium ophthalmic solution, 0.1%, or a combination of these factors, include corneal erosion, corneal infiltrates, corneal perforation, corneal thinning, corneal ulceration, epithelial breakdown, and superficial punctate keratitis, (see PRECAUTIONS, General).

Ocular
Transient burning and stinging were reported in approximately 15% of patients across studies with the use of Voltaren Ophthalmic. In cataract surgery studies, keratitis was reported in up to 28% of patients receiving Voltaren Ophthalmic, although in many of these cases keratitis was initially noted prior to the initiation of treatment. Elevated intraocular pressure following cataract surgery was reported in approximately 15% of patients undergoing cataract surgery. Lacrimation complaints were reported in approximately 30% of case studies undergoing incisional refractive surgery.
The following adverse reactions were reported in approximately 5% or less of the patients: abnormal vision, acute elevated IOP, blurred vision, conjunctivitis, corneal deposits, corneal edema, corneal opacity, corneal lesions, discharge, eyelid swelling, injection, iritis, irritation, itching, lacrimation disorder, and ocular allergy.

Systemic
The following adverse reactions were reported in 3% or less of the patients: abdominal pain, asthenia, chills, dizziness, facial edema, fever, headache, insomnia, nausea, pain, rhinitis, viral infection, and vomiting.

OVERDOSAGE
Overdosage will not ordinarily cause acute problems. If Voltaren Ophthalmic is accidentally ingested, fluids should be taken to dilute the medication.

DOSAGE AND ADMINISTRATION

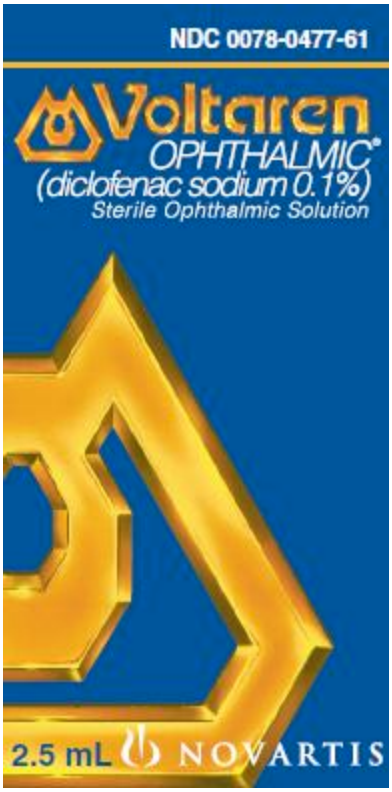
Cataract Surgery
One drop of Voltaren Ophthalmic should be applied to the affected eye, 4 times daily beginning 24 hours after cataract surgery and continuing throughout the first 2 weeks of the post operative period.

Corneal Refractive Surgery
One or two drops of Voltaren Ophthalmic should be applied to the operative eye within the hour prior to corneal refractive surgery. Within 15 minutes after surgery, one or two drops should be applied to the operative eye and continued 4 times daily for up to 3 days.

HOW SUPPLIED
Voltaren Ophthalmic 0.1% (1 mg/mL) Sterile Solution is supplied in a low density polyethylene (LDPE) white bottle with a LDPE Dropper Tip and Polypropylene grey closure. The 2.5 mL fill is supplied in a 7.5 mL size bottle. The 5.0 mL fill is supplied in a 10.0 mL size bottle.
Bottles of 2.5 mL NDC 0078-0477-61
Bottles of 5 mL NDC 0078-0478-61
Store at 15ºC to 25ºC (59º to 77ºF).
Dispense in original, unopened container only.
Made in Canada
Manufactured for:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936
REV: JULY 2009 T2009-94

PRINCIPAL DISPLAY PANEL
Package Label – 2.5 mL
RX Only NDC 0078-0477-61
VOLTAREN® Ophthalmic
(diclofenac sodium 0.1%)

Sterile Ophthalmic Solution



PRINCIPAL DISPLAY PANEL
Package Label – 5 mL
RX Only NDC 0078-0478-61
VOLTAREN® Ophthalmic
(diclofenac sodium 0.1%)
Sterile Ophthalmic Solution